Lutein Esters to Reduce the Risk of Age-Related Macular Degeneration and Cataracts

Final Report
November 15, 2004

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INTRODUCTION

The Food and Drug Administration (FDA) was petitioned for the following food-related health claims:

1) Consumption of 12 mg Xangold lutein esters per day may reduce the risk of age-related macular degeneration.

2) Consumption of 12 mg Xangold lutein esters per day may reduce the risk of cataract formation.

Background

Lutein is a yellow carotenoid found in egg yolk, maize, leafy green vegetables such as kale and spinach, and certain colored fruits such as melon and guava.[1] The typical American diet is estimated to contain about 1,500 mcg of lutein in foods consumed in a 24-hour period; national surveys indicate that the average American consumes about 2,000 mcg of lutein per day.[2]

Lutein is one of two main carotenoids (along with zeaxanthin) present in the human retina and, in particular, the macula, making up the macular pigment. Although the role of the macular pigment is not fully understood, it is hypothesized that its functions include limitation of the damaging effects of blue light through its absorption, reduction of the effects of light scatter and chromatic aberration on visual performance, and anti-oxidative protection against the adverse effects of photochemical reactions.[1]

Age-related macular degeneration

Age-related macular degeneration (AMD) is a progressive deterioration of the macula, the central portion of the retina. The macula is responsible for high-resolution visual acuity and AMD often leads to loss of detailed object recognition in the central field of vision. There are two forms of AMD: non-exudative ("dry") and exudative ("wet"). The non-exudative form of AMD accounts for about 90% of cases and is characterized by deposits of cellular debris, referred to as drusen, and changes in the photoreceptor cells and the retinal pigment epithelium. The progression of non-exudative AMD is slow and painless and often develops unnoticed. The main symptom is a gradual increase in difficulty of fine discriminate tasks. There is no effective treatment or prevention for non-exudative AMD.

Exudative AMD comprises about 10% of all cases of AMD and results from neovascular growth under the macula. Fluid and blood loss from the underlying blood vessels damage the photoreceptor cells of the macula and reduce visual acuity. The main symptoms are central blurring and distortion of sudden onset. Progression of exudative AMD can be rapid and can result in significant loss of visual acuity within weeks. Laser photocoagulation of the underlying blood vessels can reduce and retard the loss of visual acuity associated with this form of AMD.[3]

AMD is the number one cause of irreversible loss of vision in people age 65 years and older in the US. The prevalence of AMD is increasing as the population ages. It is estimated that 1.6% of the population in the 50- to 65-year-old age group is affected, increasing to 30% in the over-75 year old age group. Significant risk factors for development of AMD include

smoking, female sex, hypertension, and family history of AMD. Whites are much more likely to lose vision from AMD than blacks. In 2000, AMD accounted for 54% of blindness in whites in the US, compared with 4.4% of blindness in blacks.[4]

Proposed mechanisms by which lutein may prevent AMD are as antioxidants to oxidative stress from metabolism, and reducing the oxidative effects of blue light by filtering short wavelengths of light.[5]

Cataracts

Cataracts are the second leading cause of blindness in the US,[4] and cataract extraction is the most frequently performed surgery in the US.[6] The prevalence of cataract in the US is estimated to be about 5% by age 65, 50% in people ages 65 to 74, and 70% in people age 75 and older.[7] In blacks in the US, cataracts are the number one cause of blindness.[4]

A cataract is defined as a clouding of the crystalline lens of the eye. The clouding prevents light from passing through the lens to properly focus on the retina, resulting in cloudy or blurry vision, glare, halos, decreased night vision, a perception that colors are faded, double vision, need for brighter light when reading, and frequent changes in eyeglass prescriptions. The only treatment is cataract extraction, in which the cloudy lens is removed and a permanent artificial lens is inserted.[6]

The pathogenesis of cataract is not completely understood. Significant risk factors include genetic predisposition, age, female sex, exposure to Ultraviolet-B radiation, diabetes, alcohol use, and smoking.[6,7] Types of cataracts include nuclear (the most common leading to surgery), cortical, posterior subcapsular, and mixed. Each type has a different location in the lens and different risk factors for development. In the US, whites are more likely to have nuclear and posterior subcapsular opacities, and blacks are more likely to have cortical cataracts.[6]

The hypothesis that increased intake of lutein may prevent the development of cataracts is based on the assumption that the development of cataract is a consequence of decades of accumulated damage to lens proteins. Lutein and zeaxanthin are the predominant carotenoids found in the human lens, and increasing levels of these carotenoids in the lens through the diet may prevent or delay oxidative damage that contributes to cataract formation.[8]

METHODS

The methodology for reviewing health claim petitions, including topic evaluation, literature search, study eligibility criteria, and study evaluation, were established by the Oregon Health & Science University Evidence-based Practice Center (EPC), the Tufts-New England Medical Center EPC, the Agency for Healthcare Research & Quality, and the FDA prior to the evaluation of this health claim petition. The methodology merges elements of processes used by the EPCs, an interim FDA grading system, and the US Preventive Services Task Force.[9]

Health Claim Review

The review team included a nutritionist, a family practice physician, and an ophthalmologist, in addition to EPC staff, all of whom have experience in systematic reviews. The EPC worked in consultation with AHRQ and FDA representatives to clarify issues related to

the proposed health claims, the populations, conditions, and outcomes of interest, and the relevant study designs needed to assess the health claims.

Literature Search

The Oregon EPC conducted supplemental literature searches of Medline, CINAHL (Cumulative Index to Nursing & Allied Health Literature), the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, the Database of Abstracts of Reviews of Effectiveness (DARE), and Embase (see Appendix A for search strategies). We also conducted broad searches of the International Bibliographic Information on Dietary Supplements (IBIDS) database and the UK Foods Standards Agency web site (using the term *lutein*), and hand-searched reference lists of selected articles.

Study Selection

We reviewed for inclusion the full-text of all articles submitted by the petitioner. We examined the titles and abstracts of citations identified through supplemental searches and retrieved and reviewed the full-text articles of potentially relevant citations. All citations and articles were assessed independently by at least two reviewers; disagreements were resolved by consensus. To determine study eligibility, we applied the following criteria:

Population

- Generally healthy population
- All demographic groups

Exclusions:

- Patients with macular degeneration or cataracts
- Patients with other conditions affecting vision (e.g., retinitis pigmentosa)

Intervention

- Intake of lutein esters

Exclusions:

- Combination supplement or food study where the effect of lutein could not be separated from other substances
- Study in which the amount of lutein could not be quantified

Outcomes

- Measures of visual acuity
- Surgery for cataract extraction
- Measures of lens opacity (e.g., Lens Opacity Classification System)
- Retinal drusen changes
- Atrophic changes characteristic of macular degeneration

Exclusions:

- Intermediate outcomes, specifically

- Retinal pigment changes
- Serum lutein levels
- Lens concentration of lutein

There is evidence that increasing lutein intake may increase the macular pigment.[10] However, the link between increased macular pigment and the prevention of AMD or the link between increased levels of lutein in the lens and cataracts is not established. For this reason, we excluded studies that reported only retinal pigment changes or changes in lens levels of lutein.

Study designs

- Controlled trials
- Observational studies

Exclusions:

- Letters, editorials, etc (no original data)
- Abstract or poster
- Case series with <5 patients
- Non-English language articles (except when a translation is provided by the petitioner)
- Non-human subjects

Reporting Results

Two reviewers independently abstracted data and assessed the quality of each included study. Results were compared and disagreements resolved by consensus, with the input of a third reviewer if necessary.

The data from each study are reported in evidence tables that provide detailed study data, summary tables that provide a succinct overview of the data for each health claim, and descriptively in the text.

Evidence tables

The evidence tables describe the study design, duration, eligibility criteria, population characteristics, method of measuring lutein intake, comparator, followup rate, outcome definitions, methods and timing of outcome measures, confounders controlled for in analyses, and results.

The following results are reported in the evidence tables: The risk of cataract extraction, incident cataract, lens opacities, or measures of macular degeneration as the relative risk or odds ratio by quintile of lutein intake compared with the lowest quintile of intake. The 95% confidence intervals for each quintile and p-values for trends are also reported.

Summary tables

For each health claim, data from included studies are synthesized in Summary Tables. These tables were developed by condensing information from the evidence tables and are designed to facilitate comparisons and synthesis across studies. Summary tables include information regarding study design, study size, intervention and control, outcome measures,

results and methodological quality. A study with multiple outcomes may be presented multiple times within tables.

For each outcome the following information from the corresponding summary table is presented using a summary matrix:

- methodologic quality
- applicability of the population
- the overall effect, reported as:
  - ++ A statistically significant ($p<0.01$), beneficial effect.
  - + A statistically significant ($p<0.05$), beneficial effect.
  - 0 No effect
  - - A worsened effect

Quality Grading of Evidence

To assess the quality of the studies, and thus to provide readers with an additional means to interpret the value of the evidence, we have applied a 3-category grading system (A, B, C) to each trial. This scheme defines a generic grading system for study quality that is applicable to each type of study design.

A Least bias; results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal randomized study; clear description of the population, setting, interventions and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20% dropout; clear reporting of dropouts; and no obvious bias.

B Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria in category A. It has some deficiencies but none likely to cause major bias. Study may be missing information making assessment of the limitations and potential problems difficult.

C Significant bias that may invalidate the results. A study with serious errors in design, analysis, or reporting. These studies may have large amounts of missing information or discrepancies in reporting. All non-controlled studies are given this grade.

Because observational studies do not have randomization, allocation concealment, and blinding, a core set of criteria different from that used for RCTs was defined for these studies. Criteria to assess the quality of prospective cohort studies were:

- Unbiased selection of the cohort (prospective recruitment of subjects)
- Sufficiently large sample size
- Adequate description of the cohort
- Use of appropriate exposure/intervention measure
- Use of appropriate outcome measure
- Adequate follow-up period
- Completeness of follow-up

- Analysis (multivariate adjustments)
- Error-free reporting of results

Criteria used to assess the quality of case-control studies were:

- Valid ascertainment of cases
- Unbiased selection of cases
- Appropriateness of the control population
- Verification that the control is free of outcome of interest
- Comparability of cases and controls with respect to potential confounders
- Validated dietary assessment method
- Appropriateness of statistical analyses

Assignment of Overall Grade

The topic experts assigned each proposed health claim an overall grade based on the interpretation of the overall evidence using the following system:

A Significant Scientific Agreement/High level of comfort

Grades for qualified claims:

B Moderate/good level of comfort
C Low level of comfort
D Extremely low level of comfort
F Claim is very unlikely to be valid—high-quality evidence of NO effect.
I Little or no credible evidence for the intended population, insufficient to determine the validity of the claim.

RESULTS

In addition to the articles submitted by the petitioner, seven articles from supplemental searches were retrieved for full-text review.

After full-text review, we included two cohort studies, two case-control studies, and one cross-sectional study for the claim about AMD. We included five cohort studies and one case-control study for the claim about cataracts. We identified no clinical trials that met inclusion criteria.

Health Claim 1: Lutein to reduce the risk of age-related macular degeneration

Overview of the Body of Literature

We included five observational studies about the effect of the consumption of lutein esters on the risk of developing AMD. Details of the design, characteristics, and outcomes of these studies are shown in Evidence Table 1.

The best evidence was derived from two population based, prospective cohort studies: the Beaver Dam Eye Study (1998)[11] and the Blue Mountains Eye Study (2002).[12] Each study was carried out in distinct cohorts that were 99% white, free-living, urban, middle-aged and older, men and women. Both studies estimated typical dietary intake of lutein with validated food frequency questionnaires and then measured incident ARM after 5 years. The median values for each quintile of lutein intake, adjusted for energy intake, ranged from 294 to1005 μg/1000 kcal/d in the Beaver Dam Eye Study to 151 to 719 μg/1000 kcal/d (288 μg/d to 1466 μg/d) in the Blue Mountains Eye Study. Neither study examined intake of lutein in supplement form because lutein as a dietary supplement was not commercially available at the time the studies were conducted. The Beaver Dam Eye Study[11] cohort (n=1586) resided in south central Wisconsin, was between 43-84 years of age and was 55.5% female and 44.5% male. The Blue Mountains Eye Study[12] cohort (n=1989) resided west of Sydney, Australia within two adjacent postal code regions, was ≥49 years of age, and was 56.9% female and 43.1% male.

Although the timeframe of the two studies overlapped, the design and conduct of the Blue Mountains Eye Study was strongly informed by the Beaver Dam Eye Study. As a result, the Blue Mountains Eye Study closely replicated the major components of the Beaver Dam Eye Study rather than testing an independent design.

Both studies were judged to have "moderate" internal validity (grade B) and each was rated grade "II" for applicability.

A cross-sectional study[13] and two case-control studies[14, 15] were included but judged to be of low internal validity (grade C) because they did not collect dietary intake data prospectively (i.e., intake data were collected after outcome status was known). We considered this a serious design flaw because it is impossible to determine whether the subjects' lutein intake (or recall of intake) was influenced by their condition. For example, a person diagnosed with AMD may believe that his or her intake of certain nutrients was the cause of the AMD, and may consequently underestimate actual intake, leading to the false conclusion that low lutein intake is associated with greater risk of AMD. Because of this potential for differential recall bias, these studies are not considered further, but their results are displayed in evidence tables and summary tables for the information of the reader. Although these studies are suggestive of a link between diet and AMD, we looked for validation of these findings in prospective studies.

Outcome measures

Both cohort studies used stereoscopic 30° color fundus photographs taken at baseline and after 5 years of follow-up to analyze for a spectrum of lesions thought to characterize early and later stages in the development of age-related maculopathy (ARM) and AMD. This array of lesions included drusen size and type, retinal pigment epithilium depigmentation, increased retinal pigmentation, pure geographic atrophy and exudative, age-related macular degeneration.

In the Beaver Dam Eye Study,[11] analysts, blinded to participant characteristics, conducted side-by-side comparisons of baseline and follow-up photographs for each eye to determine the appearance of a lesion at follow-up that was absent at baseline. Only individuals who were free of specific lesions at baseline were included in the incident analysis of a specific lesion type at follow-up. Incidence of large (>125 μm) drusen (n=1,361) and retinal pigmentary abnormalities

(n=1,405), early ARM lesions associated with increased risk of late stage AMD, were analyzed independently. In addition, incidence of "any" ARM lesion (n=1279), including soft, indistinct drusen or any type of drusen associated with hyper- or hypo-pigmentation was analyzed collectively.

The Blue Mountains Eye Study[12] examined three different outcomes as measures of macular degeneration: incident AMD, incident early ARM, and at risk for incident early ARM. Incident AMD was defined as the presence of AMD in either eye at follow-up in individuals without AMD in both eyes at baseline. AMD was characterized by having two late ARM lesions: geographic atrophy involving the fovea and neovascular ARM (as defined by the International Classification and Grading System for ARM and AMD). Incident early ARM was defined as the presence of early ARM in either eye at follow-up of persons without either AMD or early ARM in both eyes at baseline, and also without AMD at follow-up. Early ARM was characterized as the absence of AMD and either (1) large (>125 μm) indistinct soft or reticular drusen or (2) both large, distinct, soft drusen and retinal hyper- or hypo-pigmentation within the macular area. Subjects at risk for incident early ARM included those who had at baseline distinct soft drusen or retinal pigmentary abnormalities alone, which were not considered early ARM at the time. In addition to incidence, progression of early to more advanced ARM lesions was measured as a change from Age-related Eye Disease Study (AREDS) classification of 1 or 2 at baseline to 3 or 4 at the 5-year follow-up examination. The AREDS Research Group[16] defined Category 1 as free of ARM abnormalities with fewer than 5 small drusen (<63 μm) and total drusen area less than 125 μm. Category 2 includes mild or borderline ARM abnormalities (multiple small drusen, single or non-extensive intermediate drusen (63-124 μm), pigment abnormalities or any combination of these. Category 3 includes at least 1 large drusen (125 μm), extensive intermediate drusen, or geographic atrophy that does not involve the center of the macula, or any combination of these. Category 4 includes advanced AMD involving geographic atrophy of the center of the macula or features of choroidal neovascularization, or photocoagulation for AMD.

Results

The two population-based prospective cohort studies found no association between dietary lutein intake and reduced risk of ARM/AMD.

In the Beaver Dam Eye Study[11] none of the participants who were free of ARM at baseline developed late ARM (or AMD) characterized by neovascular or exudative macular degeneration or geographic atrophy, during the 5-year follow-up period. Therefore, all incident ARM cases in this study were early ARM characterized by large drusen or pigmentary abnormalities. There was no significant trend of inverse association over all quintiles of typical dietary lutein intake either in the distant past or at baseline and the risk of large drusen ($p = 0.86$ and $p = 0.87$, respectively) or pigmentary abnormalities ($p = 0.68$ and $p = 0.67$, respectively). Likewise, there was no significant trend of inverse association between the typical dietary intake of lutein and the incidence of any ARM (data not shown).

In the Blue Mountains Eye Study [12] 21 participants developed neovascular or exudative macular degeneration or geographic atrophy, during the 5-year follow-up period. However, there was no association between baseline intake of lutein or any other antioxidants examined and incident AMD (data not reported). Likewise, there was no significant trend of inverse association over all quintiles of typical dietary lutein intake and the risk of early ARM ($p = 0.90$ or $p=0.93$) when adjusted for age and gender or in a multivariate analysis, respectively. Nor was

there any significant association between dietary lutein intake and progression from early to late stage ARM (AREDS ARM categories 1 or 2 to categories 3 or 4; results not shown).

Quality

Details of the quality assessment of the studies of AMD are shown in Evidence Table 2.

The Beaver Dam Study was rated moderate or grade "B" for internal validity. This rating was based on the recruitment and selection of a cohort of non-institutionalized, older men and women residing in a single township in Wisconsin. The population was identified by private census and recruited through letters from primary care providers and the principal investigator of the study with follow-up telephone communication. Although possible, the risk of recruitment bias is considered low. The resultant sample size of 1,586 was powered for a study of early ARM, not AMD. Although early ARM has been linked to AMD, it is not a defined risk factor for AMD. The follow-up rate at 5 years was 81% of known survivors and 79.4% overall, and was considered borderline adequate. No comparison was made between those individuals lost to follow-up and those completing the follow-up examination, which leaves open the possibility of sampling bias.

Lutein intake (exposure) was estimated with a validated FFQ at a single point in time for baseline and 10 year past intake. Administration of a single FFQ at a single point in time to estimate nutrient intake is considered to be of moderate quality. The authors report lutein intake indexed to energy intake but did not report absolute, unadjusted lutein intake. However, when a nutrient selectively affects an organ system that is uncorrelated with body size (e.g., the retina) or if physical activity does not affect its metabolism, absolute intake may be most relevant.[17] The authors argue that adjusting for energy intake minimizes extraneous variation due to general under-or over-reporting of food intake and to account for differences in body size and physical activity. However, by doing so the ability to assess the impact of lutein on prevention of ARM may be limited. Reporting and analyzing lutein intake indexed to energy intake would be a more significant issue if higher amounts and a greater range of lutein intake had been observed within the cohort.

Stereoscopic 30° color fundus photographs, a research tool used to classify, quantify, and document lesions associated with ARM/AMD, were compared at baseline and follow-up by research staff masked to participant characteristics. It is assumed that the study participants and other research staff involved in data collection were also masked to the results of the baseline eye examination, however, these details are not provided. If masking of research staff and participants was not maintained then data ascertainment and recall bias is a possibility.

The adequacy of the 5-year follow-up period to determine incident ARM and AMD is uncertain. Pigmentary abnormalities, like large soft drusen, have been observed to predict incident late ARM over 5 years,[18] however the incidence rate from a disease free state is not well established. In the studies described here, there were no incident cases of AMD in one study and 21 cases (insufficient for analysis) in the other.

Odds ratios for quintiles of lutein intake were calculated from logistic regression models adjusting for multiple known and possible risk factors. This multivariate regression analysis was considered appropriate and there were no apparent reporting errors.

Because the methodology of the two studies was similar, the internal validity issues discussed in reference to the Beaver Dam Eye Study are also relevant to the Blue Mountains Eye Study. We also rated the Blue Mountains Eye Study grade "B" for internal validity. The cohort was recruited from the older, non-institutionalized male and female population residing within

two adjoining urban postal code areas in the Blue Mountains area in New South Wales, Australia. The population was identified by door-to-door visits using Australian National Census data and was judged to be sufficiently comprehensive to result in minimal recruitment bias. Individuals were excluded from analysis due to incomplete or implausible responses to the FFQ (n=343). These members of the initial cohort tended to be older, to have difficulty walking, and to be a current smoker. The final cohort was comprised of 1989 individuals and represented 75% of known survivors. This follow-up rate was considered inadequate (>20% dropout rate) and may contribute to outcome ascertainment bias. However, data was presented to illustrate that there were no differences in baseline lutein intake or other antioxidant intakes between those who completed the study and those who were lost to follow-up.

Lutein intake at baseline was estimated with a single validated FFQ administered by in-person interview and reported as absolute, unadjusted intake as well as energy adjusted intake. Data obtained from the administration of a single FFQ at a single point in time to estimate nutrient intake is considered to be of moderate quality.

Stereoscopic 30° color fundus photographs taken at baseline and follow-up were graded by research staff masked to participant characteristics using the Wisconsin Age-Related Maculopathy Grading System and the AREDS ARM categories, accepted methods of classification and diagnosis. The adequacy of the 5-year follow-up period is as described above. The multivariate regression analysis was considered appropriate and there were no apparent reporting errors.

Applicability

The applicability of each study was rated moderate (II) (Evidence Table 3). Both studies included middle-aged and older men and women; individuals < 43 or < 48 years of age were not eligible for participation in the two cohorts. Although AMD occurs at higher rates in white compared to black US populations, both studies were conducted in cohorts that were 99% white. Neither study included a broad sample of racial and ethnic groups. The range of dietary lutein intake in the two cohorts studied was low and narrow. Each study used as its comparator the quintile of lowest dietary lutein intake, which represents a limited exposure to dietary lutein. The median lutein intake of the lowest quintile was 151 µg/1000 kcal/d (288 µg/d or ~14-19% of the average US intake (~1500-2000 µg/d)) in one study and 294 µg/1000 kcal/d in the other. The median lutein intake of the highest quintile was 719 µg/1000 kcal/d (1466 µg/d or 73–97% the average US intake) in one study and 1006 µg/1000 kcal/d in the other. So, while there were absolute differences in median lutein intake among the quartiles in each study, the lutein intake of the highest quartiles were similar to the average US intake, which in itself is considered to be low, and did not encompass the 12 mg/d of supplemental lutein specified in the health claim. Therefore the levels of lutein intake observed in these two studies, and the differences between the upper and lower quartiles, were most likely not sufficient to answer the study question.

Summary of the Body of Literature

The methodological quality, applicability, and detected effects of the studies are summarized in Table 1.

Table 1. Studies of the association of dietary lutein intake and risk of macular degeneration

Quality	Study/Cohort (Author, year)	N	Duration	Outcome	Dietary Assessment	Results Lutein and zeaxanthin intake (mcg/1000 kcal/day) by quintile Odds Ratio (95% CI)[1]	Trend P-value	Overall Effect[3]
A	NA							
B	Beaver Dam (Vanden-Langenberg, 1998)	1586	5 years	Large Drusen	FFQ	294 / 421 / 537 / 691 / 1005 1.00 / 0.76 (0.40, 1.50) / 0.76 (0.40,1.50) / 0.93 (050, 1.70) / 0.93 (0.50, 1.80) (Based on intake in past year, distant intake similar)	NS (0.86)	0
				Retinal pigmentary abnormalities		294 / 421 / 537 / 691 / 1005 1.00 / 0.82 (0.30, 2.00) / 0.92 (0.40,2.10) / 1.13 (0.50, 2.60) / 0.84 (0.30, 2.0) (Based on intake in past year, distant intake similar)	NS (0.87)	0
				Any early ARM		No association (data not reported)	NR	0

B	Blue Mountains (Flood 2002)	1989	5 years	Incident AMD	FFQ	21 cases (no association with baseline intake, data not reported)	NR	0
		1989	5 years	Incident Early ARM	FFQ	151 259 351 478 719 1.00 0.90 (0.50,1.5) 0.80 (0.5,1.4) 0.70 (0.4,1.3) 1.00 (0.6,1.6)	NS (0.93)	0
		1709	5 years	Incident at risk for early ARM[2]		206/1709 (12%); (analysis based on only those who completed FFQ and progressed from category 1 or 2 to category 3 or 4; n=162). No association with baseline intake; data not reported.	NR	0
C	NHANES III (Mares-Perlman, 2001)	8,222	NA	Soft drusen	FFQ	Adjusted OR (95% CI) for soft drusen in high vs low quintiles of lutein and zeaxanthin in the diet (intake by quintile not reported): Total: 1.4 (1.0, 1.8) ages 40-59: 1.2 (0.6, 2.3) ages 60-79: 1.3 (0.9, 1.9) ages >80: 2.4 (1.3, 4.4)	NR	0 (+ for those over age 80)
C	Eye Disease Case-Control Study (Seddon,1994)	876	NA	AMD	FFQ	Adjusted OR (95% CI) for exudative AMD by quintile of energy-adjusted nutrient intake (lutein/zeaxanthin median intake): 560.8 1211 1708 2487 5757 1.00 1.14 (0.7, 1.8) 0.84 (0.5, 1.3) 0.77 (0.5, 1.2) 0.43 (0.2, 0.7)	<0.001	++
C	Snellen, 2002	138	NA	AMD	FFQ	Adjusted OR (95% CI) for AMD by quartile of intake (mcg of intake not reported): Highest High Low Lowest 1.00 3.4 (0.9, 12.3) 3.6 (1.0, 12.9) 5.3 (1.5, 18.4)	NR	+

[1]Odds Ratio in each study adjusted for main confounders as reported in article.
[2]Progression from Age-related Eye Disease Study (AREDS) (REF) category 1 or 2 to 3 or 4
[3]Overall Effect reported as:

- ++ A statistically significant ($p<0.01$), beneficial effect.
- + A statistically significant ($p<0.05$), beneficial effect.
- 0 No effect

- A worsened effect

[4]Intake assessment for both baseline (one year period immediately prior to FFQ) and distant past (one year period 10 years prior to FFQ) was made during the same interview at baseline.
[5]Intake as µg/4.18 MJ/d
*Association was no longer significant after lutein intake was mutually adjusted with intake of multiple other nutrients, nor after pairwise adjustment with vitamin C, while vitamin C remained significantly associated in both models.
Abbreviations: 95% CI = 95% Confidence Interval; NS = Not statistically significant ($p \geq 0.05$)

Aggregate Quality of the Evidence

The aggregate quality of the evidence for an inverse association between intake of lutein and risk of development of AMD or early ARM was rated as moderate or "B". Table 2 (below) illustrates these findings. Two population-based prospective cohort studies found no association between dietary lutein intake (at the range of lutein intake reported) and reduced risk of ARM/AMD. The results, showing no effect of lutein intake on risk of ARM/AMD, were consistent between the studies. Internal validity for each study was judged to be moderate: identification and recruitment of subjects was appropriate, the methods of collecting data were considered likely to impart minimal bias. The sample sizes were adequate for the primary outcomes, but one study was powered only to detect ARM, not AMD. Both studies evaluated outcomes after a 5-year follow-up interval, a time frame that may be too short to assess incident AMD, and rates of followup were below 80%.

Two case-control studies[14, 15] found a decreased risk of AMD with higher lutein intake, and a cross-sectional study[13] found decreased presence of soft drusen in subjects over age 80 with the highest lutein intake (although not in the overall study sample). Because dietary data were not collected prospectively in these studies (i.e., intake data were collected after outcome status was known), these results are not considered in the assessment of the aggregate quality of the evidence.

Aggregate Applicability of the Evidence

The applicability of each study was rated moderate or "II" and the aggregate applicability of the two studies was rated "II". Neither study addressed a broad sample of racial or ethnic groups; both cohorts were 99% white. Both studies limited enrollment to individuals who were middle aged (>43 or >48 years of age) and older. The ranges of lutein intake were low and narrow and did not include the amount of lutein referenced in the health claim (12 mg per day).

Table 2. Summary matrix: association of dietary lutein intake and risk of macular degeneration

	Methodological Quality								
Applicability		A: High	B: Moderate				C: Low			
	I								
	II		Study	Outcome	N	Effect[1]	Study	Outcome	N	Effect[1]
			Flood, 2002	Incident AMD	1,989	0	NHANES, 2001	soft drusen	8,222	0
			Vanden-Langenberg, 1998	Incident AMD	1,586	0	Seddon, 1994	AMD	876	++
							Snellen, 2002	AMD	138	+
	III									

[1]Overall Effect reported as:

++ Astatistically significant ($p<0.01$), beneficial effect.
+ A statistically significant ($p<0.05$), beneficial effect.
0 No effect
- A worsened effect

Overall Grade

The overall grade for the health claim that "Consumption of 12 mg Xangold lutein esters per day may reduce the risk of age-related macular degeneration" was judged to be "I." This grade is based on the aggregate quality of the evidence (moderate), the aggregate applicability of the evidence (moderate, or "II") and the lack of effect of dietary lutein intake on risk of developing AMD/ARM in studies of moderate methodological quality. Two moderate quality prospective cohort studies were included in this review and neither found an effect of dietary lutein intake on prevention of AMD. The more recently reported study, the Blue Mountains Eye Study, was heavily informed by the previous study, the Beaver Dam Eye Study. The findings reported in these two studies were consistent and may be due, at least in part, to the low and narrow range of dietary lutein intake of the cohorts observed. Furthermore, evidence in support of this health claim may be limited in that neither study examined lutein intake at the level of the general US population or populations known to consume high amounts of dietary lutein, in the form of dietary supplements, or at the level specified in the health claim (12 mg/day).

RESEARCH RECOMMENDATIONS

The evidence is insufficient to support the claim that intake of dietary lutein may reduce the risk of AMD. However, the limited number of studies available for review, and the features of these studies may have limited the ability to detect a relationship between lutein intake and ARM/AMD. Specifically, the limited and low ranges of lutein intake observed, the older populations studied, and the relatively short duration of follow-up reduced the applicability of the results. To gain a better understanding of the protective role of lutein on ARM and AMD, future research should include well-designed prospective cohort studies that enroll a younger cohort, expanded ethnic and racial representation, and include populations known to routinely consume higher amounts of dietary and/or supplemental lutein. The period of follow-up should extended beyond 5 years to better assess and distinguish short-term and long-term effects of lutein intake and to capture what may be an independent effect of lutein on later stages of ARM/AMD. Additional research should address the differential effect of lutein consumed as food versus supplement on ARM/AMD, if any, and the safe upper-levels of lutein; short-term (140 d) intakes of up to 30 mg of lutein per day have been reported.

Until recently, prospective cohort studies capturing chronically high lutein intakes were limited in scope due to the low consumption of lutein in the typical US diet. Now, lutein is available over-the-counter as a dietary supplement as a single ingredient or in combination with other vitamins and minerals. In addition, in 2003 lutein was designated as Generally Recognized As Safe (GRAS) by the FDA and approved for use as a food additive in a variety of foods and beverages. Addition of lutein to the food supply as a dietary supplement or food additive will likely increase the consumption of lutein in the US and extend the potential of prospective population based cohort studies to define relationships between lutein intake and age-related macular degeneration.

Health Claim 2: Lutein to reduce the risk of cataracts

Overview of the Body of Literature

Evidence for the effect of consumption of lutein esters on the risk of cataract formation was derived from five observational studies. Details of these studies are described in Evidence Table 4 (characteristics and results), Evidence Table 5 (internal validity), and Evidence Table 6 (external validity).

The best evidence comes from four cohort studies carried out on three distinct cohorts.[8, 19-22] All of the studies examined dietary intake of lutein as measured by food frequency questionnaires. None of the studies examined intake of lutein in the form of supplements. The studies examined three different outcomes as measures of cataract formation. These outcomes were: incident extraction of cataract;[19, 21] incident cataract;[20] and lens opacity at the end of the study period.[8, 22] Additionally, the studies examined three different cataract subtypes (nuclear, cortical and posterior subcapsular), corresponding to the three metabolically distinct zones of the lens. The subtypes occur with different frequencies and may have different etiologies. Two studies examined all three subtypes combined, and also analyzed nuclear and posterior subcapsular cataracts separately.[19, 21] One study examined each of the three subtypes separately,[8, 22] and, one study was of nuclear cataracts only.[20] Follow-up periods ranged from 5 years to 15 years.

Two studies were conducted in the Nurses' Health Study (NHS) cohort. One of these was based on the entire NHS cohort.[21] The other, called the Nutrition and Vision Project (NVP), was based on a subset of the NHS cohort made up of women living in a single metropolitan area.[8, 22] One study was conducted in the Health Professionals Follow-up Study (HPFS) cohort,[19] and the fourth was conducted in the Beaver Dam Study cohort.[20]

The size of the study populations ranged from 478 to 77,466. All of the studies were conducted in the United States. Two studies were of women only,[8, 21, 22] one was of men only,[19] and one included both women and men.[20] All included predominantly white populations.

Three of the four cohort studies had good internal validity (grade A)[8, 19, 21, 22] and one was rated grade C.[20] Because the populations studied were representative only of relevant subgroups, and not of the entire target population, each was rated grade "II" for applicability.

One case-control study[23] met inclusion criteria, and was judged to be of low internal validity (grade C) because information on dietary intake of lutein was not collected prospectively (i.e., intake data were collected after outcome status was known). We considered this a serious design flaw because it is impossible to determine whether the subjects' recall of lutein intake was influenced by their condition. For example, a person with known cataracts may believe that his or her intake of certain nutrients was the cause of the cataracts, and may consequently underestimate actual intake, leading to the false conclusion that low lutein intake is associated with greater risk of cataracts. Because of this potential for differential recall bias, this study is not considered further, but its results are displayed in evidence tables and summary tables for the information of the reader.

Study Summaries

The included studies are summarized by outcome measure, below.

Cataract extraction

Two good quality (grade A) prospective cohort studies examined the relation between dietary lutein intake and cataract extraction.[19, 21] These studies were of a similar design, but each was carried out in a different cohort.

Brown[19] studied a baseline population of 36,644, predominantly white, male health professionals (dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians) between 45 and 75 years of age who were enrolled in the Health Professionals Follow-up Study (HPFS) cohort. An unspecified number of men in the HPFS cohort were later included in the Brown (1999) study as they reached 45 years of age, for a total of 307,259 person-years of follow-up over the 8-year study period.

The validated FFQ used to measure dietary lutein intake was mailed to all members of the HPFS cohort in 1986 and again every two years. The FFQ asked about intake during the previous year. For its primary analysis, Brown (1999) used only the 1986 baseline FFQ to calculate lutein intake. They also performed an analysis using the same baseline intake data (from the 1986 FFQ) for the first half of the 8-year study period, and the average of data from two FFQs (the 1986 baseline and the 1990 study midpoint) for the second half of the study period. The outcome of cataract extraction was measured prospectively based on participant self-reporting on biennial questionnaires, and confirmed by the subject's ophthalmologist and medical record review. All cataract subtypes were included and not differentiated for the primary analyses. Sub-analyses by type of cataract were also reported. Analyses were adjusted for multiple known and possible risk factors, including age, cigarette smoking, and diabetes.

The median values for each quintile of energy-adjusted lutein intake ranged from 1300 µg/day to 6871 µg/day. A total of 840 cases of cataract extraction were reported. The study found a modest but non-significant decrease in risk of cataract extraction in the top quintile of lutein intake compared with the bottom quintile of intake (RR = 0.81; 95% CI: 0.65, 1.01). The test of trend of decreasing risk of first cataract extraction with increasing intake of lutein was significant (P = 0.03).

Brown reports that the results of analyses using cumulative intake data from two FFQs (as described above) were similar to the results of analyses using the baseline intake alone. For this analysis, they only report the multivariate RR of the top quintile of lutein intake compared with the bottom quintile of intake (RR = 0.78; 95% CI: 0.62, 0.98), and the P for trend = 0.01. Comparison of the top decile to the bottom quintile found a similar and non-significant decrease in risk (RR = 0.78; 95% CI: 0.59, 1.03; P for trend = 0.02). Analysis was also conducted using each of the three cataract subtypes as the outcome variable. After excluding those subjects with more than one type of cataract, or for which subtype information was not available, there were 207 nuclear, 136 posterior capsular (PSC), and 46 cortical cataracts. No difference in risk was found between nuclear and PSC cataract subtypes. Data on cortical cataracts were too sparse for analysis.

Brown was rated good (grade A) for internal validity (Evidence Table 5). Selection of the study cohort appears unbiased; description of the cohort was adequate; exposure and outcome measures were appropriate; the follow-up period was adequate; and the analysis was appropriate. The dietary assessment using multiple measures of a validated FFQ over time is considered a high quality method. The study received an applicability rating of "II", reflecting a study sample that is representative of a relevant subgroup (white male health professionals) of the target

population of all healthy adults. Applicability was also limited by a lack of comparison of the background diet of the study population with that of the general US population.

Chasan-Taber[21] studied a baseline population of 50,461, predominantly white, female registered nurses between 45 and 71 years of age who were enrolled in the Nurses Health Study (NHS) cohort. As they reached 45 years of age, 27,005 additional women in the NHS cohort were included in the Chasan-Taber study, for a total of 77,466 subjects and 761,762 person-years of follow-up over the 12-year study period.

The validated food frequency questionnaire (FFQ) used to measure dietary lutein intake was mailed to all members of the NHS cohort in 1980, and an expanded version of the FFQ was mailed to all NHS cohort members in 1984. The FFQ asked about intake during the previous year.

To calculate lutein intake, Chasan-Taber used the data from the 1980 baseline FFQ alone for the first 4 years of the 12-year study period, and used the average of two FFQs (1980 baseline and 1984 follow-up) for the subsequent 8 years of the study period. The outcome of cataract extraction was measured prospectively based on participant self-reporting on biennial questionnaires sent to all NHS cohort members, and confirmed by the subject's ophthalmologist and medical record review. All cataract subtypes were included and not differentiated for the primary analyses. Sub-analyses by type of cataract were also reported. Proportional hazards models were used to adjust for multiple known and possible risk factors, including age, cigarette smoking, and diabetes.

The median values for each quintile of energy-adjusted lutein intake ranged from 1172 μg/day to 11685 μg/day. A total of 1471 cases of cataract extraction were reported. The study found a modest but non-significant decrease in risk of cataract extraction in the top quintile of lutein intake compared with the bottom quintile of intake (RR = 0.88; 95% CI: 0.75, 1.03). The test of trend of decreasing risk of first cataract extraction with increasing intake of lutein was significant (P = 0.04). It is notable that this reduced risk was less pronounced in Chasan-Taber than in Brown, despite a wider range of median intake for the top quintile versus the bottom quintile.

The study found the risk to be significantly decreased in the top decile of intake compared with the bottom quintile (RR = 0.78; 95% CI: 0.63, 0.95), and to a comparable degree as Brown.[19] When placed in a two nutrient model with carotene, the relative risks for lutein intake were reported to be slightly attenuated and no longer significant (values not reported). Analysis was also conducted using each of the three cataract subtypes as the outcome variable. After excluding those subjects with more than one type of cataract, or for which subtype information was not available, there were 388 nuclear, 314 posterior capsular (PSC), and 56 cortical cataracts. The relative risk of top quintile to bottom quintile for nuclear-type cataract was attenuated compared to total cataract (RR = 0.93; 95% CI: 0.68, 1.28), and the relative risk for posterior subcapsular cataract was more strongly inverse (RR = 0.68; 95% CI: 0.48, 0.97). Data on cortical cataracts were too sparse for analysis.

Chasan-Taber was rated good (grade A) for internal validity. Selection of the study cohort appears unbiased; description of the cohort was adequate; exposure and outcome measures were appropriate; the follow-up period was adequate; and the analysis was appropriate. The dietary assessment using multiple measures of a validated FFQ over time is considered a high quality method. The study received an applicability rating of "II", reflecting a study sample that is representative of a relevant subgroup (white female nurses) of the target population of all

healthy adults. Applicability was also limited by a lack of comparison of the background diet of the study population with that of the general US population.

Lens opacity

A good-quality (grade A) cohort study examined the relation between dietary lutein intake and lens opacities.[8, 22] The study, called the Nutrition and Vision Project (NVP), was conducted in a subset of women from the NHS cohort between 53 to 73 years of age who resided in the Boston area. Participants were recruited without regard to nutrient intake after four FFQs (routinely collected for the NHS) had already been completed. All participants then completed an additional FFQ and underwent a detailed, standardized eye examination. The results were reported in two papers; one assessing nuclear lens opacities,[8] and one assessing cortical and posterior subcapsular (PSC) lens opacities.[22] Jacques reported analysis of 478 women for nuclear lens opacities, and Taylor reported analysis of 492 women for cortical and PSC lens opacities.

Dietary lutein intake was calculated as the average intake from 5 validated FFQs that were mailed to participants and collected over a 13 to 15 year period prior to evaluation of lens opacities. The biennial FFQs assessed intake for the previous year. Photographic images were taken to measure the degree of opacification of each of the three lenticular zones. Two individual graders arrived at a consensus score using the Lens Opacity Classification System III (LOCS III). Because of difficulty in assessing features of the PSC region using images, in vivo measurements with LOCS III were used instead of the photographs for analysis of PSC opacities. The outcomes of nuclear, cortical and PSC lens opacity were each defined with a respective opalescence grade threshold (2.5 or greater for nuclear, 0.5 or greater for cortical, and 0.3 or greater for PSC). These thresholds are noted to represent early opacification and are not associated with symptoms. Odds ratios were calculated using the GEE method of logistic regression adjusting for multiple known and possible risk factors, including age, cigarette smoking, and sunlight exposure.

The median values for the second lowest to the highest quintile of lutein intake ranged from 2400 μg/day to 5600 μg/day.

Jacques[8] reported 478 cases of nuclear lens opacity, and found a moderate and significant decrease in the odds of nuclear opacities in each of the top four quintiles of lutein intake compared with the bottom quintile of intake. (Top quintile compared with bottom quintile OR = 0.52; 95% CI: 0.29, 0.91). No significant linear trend of decreasing risk of nuclear opacities with increasing intake of lutein was observed (P = 0.08). When lutein intake was mutually adjusted in a model with intake of multiple other nutrients, however, none of the associations of lutein intake and opacities remained significant. Similarly, when lutein intake was included in a pairwise adjustment with vitamin C, lutein was no longer significantly associated with nuclear opacities. Intake of vitamin C remained significantly associated with nuclear opacities in both models.

Taylor[22] identified 246 cases of cortical opacity and 86 cases of PSC opacity. Fifty-six women who had both cortical and PSC opacities are included in both categories. They found no significant reduction in the odds of either cortical or PSC opacities in any of the top quintiles of lutein intake compared with the bottom quintile of intake. No significant trend was noted between lutein intake and cortical or PSC opacities.

The NVP study[8, 22] was rated good (grade A) for internal validity. Selection of the study cohort appears unbiased; description of the cohort was adequate; exposure and outcome measures were appropriate; the follow-up period was adequate; and the analysis was appropriate. The dietary assessment using multiple measures of a validated FFQ over time is considered a

high quality method. The study received an applicability rating of "II", reflecting a study sample that is representative of a relevant subgroup (white female nurses) of the target population of all healthy adults. Applicability was also limited by a lack of comparison of the background diet of the study population with that of the general US population.

Incident cataract

One poor quality (grade C) population-based, prospective cohort study examined the relation between dietary lutein intake and incident nuclear cataracts.[20] This study followed 1354 primarily white residents of Beaver Dam, Wisconsin between 43 and 84 years of age. Subjects were both female (53%) and male (47%). Dietary lutein intake was measured using a single, validated FFQ administered in-person. During this in-person interview, participants were asked about dietary intake for the previous year, and also about intake in the distant past (a one-year period corresponding to 10 years prior to the FFQ). The interview was conducted approximately 1 month after a baseline lens photograph; a physical examination; and a standardized questionnaire to ascertain medical history, demographic characteristics and behavioral characteristics. It is not reported that the interviewer and the participant were blinded to the results of the baseline examination.

Nuclear opacities were independently assessed from photographs by two graders who were unaware of subject characteristics. Lenses were graded on a five-step ordinal scale (levels 1 to 5) using a set of standardized photographs for comparison. Levels 4 and 5 were considered "severe nuclear opacification", and levels 1 to 3 were considered not severe. Lens photographs were taken at baseline and again 5 years later. Participants were classified as having an incident cataract if both lenses were free of severe opacification at baseline, and at least one lens had severe opacification at the five-year follow-up examination. Odds ratios for quintiles of lutein intake were calculated from logistic regression models adjusting for multiple known and possible risk factors, including age and cigarette smoking.

The median values for each quintile of energy-adjusted lutein intake ranged from 298 μg/4.18 MJ/day to 1245 μg/4.18 MJ/day. A total of 246 cases of incident nuclear cataract were reported. Lyle (1999) reports a moderate and significant decrease in the odds of incident nuclear cataract in the top quintile of lutein intake compared with the bottom quintile of intake (OR = 0.5; 95% CI: 0.3, 0.8). The test of trend of decreasing risk of incident nuclear cataract with increasing intake of lutein was significant (P = 0.002). These associations were only significant, however, for dietary intake in the distant past. When analyzed for dietary intake at baseline, no significant associations were found (OR = 0.70; 95% CI: 0.4, 1.1; P for trend = 0.10).

Lyle was rated poor (grade C) for internal validity (Evidence Table 5). This rating was due principally to the potential for significant bias that was not adequately addressed in the study report. Although the study reports that the grading of opacification was blinded to subject characteristics, it is not reported that subjects or FFQ interviewers were blinded to the results of the baseline eye examination and/or the baseline medical, demographic and behavioral information. This leaves the possibility of significant differential information bias and/or recall bias. Although the relatively high number of subjects lost to follow-up (24.5%) is reported by general category, no comparison was made between those lost to follow-up and those not lost to follow-up. This also leaves the possibility of significant bias. The definition of five-year incident cataract did not distinguish between modest progression of a continuous process of opacification already present at baseline (e.g. level 3 progressing to level 4) and development of opacity in those with little evidence of opacification at baseline (e.g. level 1 progressing to level 5). Given

the nature of cataract as a gradually progressive process of opacification, this may be an appropriate definition, but as an outcome measure it has the potential to blur the extent of the possible effect of lutein intake on cataract formation. The dietary assessment using a single measure of a validated FFQ is considered a moderate quality method. The study received an applicability rating of "II", reflecting a study sample that is representative of a relevant subgroup (white residents of a single town) of the target population of all healthy adults. Applicability was also limited by a lack of comparison of the background diet of the study population with that of the general US population.

Summary of the Body of Literature

The methodological quality, applicability, and detected effects of the studies are summarized in Table 3 (below).

Table 3. Summary matrix: association of dietary lutein intake and risk of cataracts

	Study/Cohort (Author, year)	N	Duration (years)	Cataract subtype	Dietary Assessment	Outcome	Results Median lutein intake by quintile Relative Risk[1] (95% CI)	Trend P-value[2]	Overall Effect[3]
A	**HPFS** (Brown,1999)	36,644	8	All	FFQ	Cataract extraction	Single FFQ 1300 2279 3182 4342 6871 µg/d 1.00 1.00 0.98 0.83 0.81 (0.81,1.23) (0.79,1.20) (0.67,1.04) (0.65, 1.01) Cumulative (2) FFQs: Highest quintile/Lowest quintile RR = 0.78 (0.62, 0.98)	0.03 0.01	+
	NHS (Chasan-Taber, 1999)	77,466	12	All	FFQ	Cataract extraction	Cumulative (2) FFQs 1172 2064 2817 6047 11685 µg/d 1.00 1.01 0.95 0.81 0.88 (0.86,1.19) (0.80,1.11) (0.69,0.96) (0.75,1.03)	0.04	+
	NVP (Jacques,2001)	478	13 to 15	Nuc.	FFQ	Prevalent lens opacity	Average of 5 cumulative FFQs N/A 2400 3300 4300 5600 µg/d 1.00 0.45 0.49 0.39 0.52 (0.24,0.84) (0.25,0.94) (0.21,0.72) (0.29,0.91)	0.08	0

	(Taylor, 2002)	492	13 to 15	Cort PSC	FFQ	Prevalent lens opacity	Average of 5 cumulative FFQs Cortical: N/A 2400 3300 4300 5600 µg/d 1.00 0.63 (0.38,1.05) 1.30 (0.78,2.15) 1.02 (0.62,1.67) 0.86 (0.52,1.44) Posterior subcapsular: N/A 2400 3300 4300 5600 µg/d 1.00 0.61 (0.30,1.25) 0.83 (0.41,1.68) 0.29 (0.12,0.70) 0.60 (0.28,1.30)	NS NS	0
B	N/A								
C	**Beaver Dam** (Lyle,1999)	1,354	5	Nuc.	FFQ	Incident cataract	Single FFQ by in-person interview[4] Intake[5] at baseline: 298 459 600 784 1245 1.0 0.9 (0.6, 1.5) 1.0 (0.6, 1.7) 1.0 (0.6, 1.6) 0.7 (0.4, 1.1) Intake[5] in distant past: 298 459 600 784 1245 1.0 0.9 (0.6, 1.6) 0.9 (0.6, 1.7) 0.7 (0.4, 1.2) 0.5 (0.3, 0.8)	0.10 0.002	+
C	**Valero et al, 2002**	692	NA	All	FFQ	Prevalent cataract	Range of intake by quintile: </=443 >443-669 >669-993 >993-1383 >1383 µg/d 1.0 0.88 (0.54, 1.42) 0.98 (0.61, 1.56) 0.69 (0.6, 1.6) 1.00 (0.4, 1.1)	NS (0.78)	0

[1]Relative Risk as Rate Ratio (Brown 1999 and Chasan-Taber 1999) or Odds Ratio (Jacques 2001, Taylor 2002, Lyle 1999, Valero 2002). Relative Risk in each study adjusted for main confounders as reported in article.
[2]Trend for inverse association.
[3]Overall Effect reported as:
++ A statistically significant ($p<0.01$), beneficial effect.

\+ A statistically significant ($p<0.05$), beneficial effect.
0 No effect
\- A worsened effect

[4]Intake assessment for both baseline (one year period immediately prior to FFQ) and distant past (one year period 10 years prior to FFQ) was made during the same interview at baseline.
[5]Intake as µg/4.18 MJ/d

Abbreviations:

Cohorts:

HPFS = Health Professionals Follow-up Study
NHS = Nurses Health Study
NVP = Nutrition and Vision Project (subset from NHS)
Beaver Dam = Beaver Dam Eye Study

Cataract Subtypes:

Nuc = Nuclear
Cort = Cortical
PSC = Posterior Subcapsular

Other: 95% CI = 95% Confidence Interval
NS = Not statistically significant ($p>0.05$)

Aggregate Quality of the Evidence

To determine the aggregate quality of the evidence, we first rate the quality of the evidence *across studies for each outcome*, and then rate the quality of the evidence *across outcomes*. We consider both methodological quality and results. In the four studies reviewed for this health claim, three different outcome measures were used. Given the small number of studies, we did not consider each cataract subtype as a separate outcome for the assessment of aggregate quality.

The quality of evidence for the outcome of cataract extraction was rated as moderate. Two observational studies found associations of only modest strength and/or lacking statistical significance[19, 21] Internal validity was good, the results were generally consistent between the studies, and the sample sizes were adequate.

The quality of the evidence for the outcome of lens opacity was rated as low. Jacques[8] found a significant association of moderate strength for nuclear opacities that did not remain significant when adjusted for other nutrients. Taylor[22] found no significant associations for cortical or PSC lens opacities. These observational studies had good internal validity and adequate sample sizes.

The quality of the evidence for the outcome of incident cataract was rated as low. Lyle[20] found a significant moderate association for lutein intake in the distant past, but not at baseline. The internal validity was rated low. The sample size was adequate.

One case-control study[23] reported no association between the prevalence of cataract and lutein intake, but the level of this evidence is low because dietary data were not collected prospectively, and its results were not considered in the assessment of the aggregate quality of the evidence.

Given the predominantly low quality of the evidence for each outcome measure, the aggregate quality of the evidence across all three outcomes was rated as low.

Aggregate Applicability of the Evidence

Although the applicability of each study was rated moderate (II), in aggregate the studies address both genders and a geographically broader population. Still, three of the studies were limited to health professionals, none of the studies address a broad sample of racial and ethnic groups, nor did any compare the dietary intake of the study populations to that of the general US population. The aggregate applicability of the studies was, therefore, rated moderate ("II").

Overall Grade

The evidence for an association between lutein intake and cataract formation was judged to be insufficient, and the overall grade for the health claim is "I".
This grade is based on the aggregate quality of the evidence (low) and the aggregate applicability of the evidence (moderate, or "II"). Only two good quality cohort studies

and one poor quality cohort study found a modest effect that was not consistently significant. The effect was also inconsistent with respect to cataract subtype and with respect to correlated effects of other nutrients. Some of this inconsistency may be due the use of different study methods and different measures of cataract formation, and to the small number of studies for any single outcome measure or cataract subtype. Additionally, the ability to mutually adjust the effects of lutein and other nutrients may be limited by the high correlation that occurs because many nutrients are found together in foods. The evidence in support of the health claim is also limited in that none of the studies examined lutein intake in the form of dietary supplements; the levels of intake studied were lower than the level specified in the health claim (12 mg/day); and none of the studies compared intake of the study populations to that of the general US population.

RESEARCH RECOMMENDATIONS

Although the evidence is insufficient to support the claim that intake of lutein may reduce the risk of cataract formation, the small beneficial effect found in a small number of studies warrants further investigation. Future research should include well-designed, multi-center RCTs, with some specific evaluation of lutein in supplement form. Some RCTs should include a period of long-term follow-up of 10 to 12 years so that the short-term and long-term effects of lutein intake can be distinguished. Studies are needed that compare the lutein intake of study subjects with that of the general US population. Additional research should address the potential difference in effect on cataract formation between lutein intake as food and lutein intake in supplement form. And, future research should include investigation of safe levels of lutein intake.

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Evide... Table 1. Observational Studies of Lutein to Reduce ...e Risk of Macular Degeneration

Author, Year, Country Study Name	N	Study design	Duration	Eligibility criteria	Age Gender Ethnicity
Vandenlangenberg et al, 1998 US **Beaver Dam Eye Study**	1586 (completed all assessments-baseline FFQs, baseline and f/u eye exams)	Population-based prospective cohort	5 years	Non-institutionalized residents of Beaver Dam, Wisconsin aged 43-84, free of prevalent, late-stage disease at baseline and with gradable retinal photographs at both baseline and followup exams.	37.6% < age 55; 29% age 55-64, 26.1% 65-74; 7.1% 75 or older. 55.5% female ethnicity not reported, "primarily Caucasian" Entire cohort 99% white

Table 1. Observational Studies of Lutein to Reduce ...e Risk of Macular Degeneration

Author, Year, Country Study Name	N	Study design	Duration	Eligibility criteria	Age Gender Ethnicity
Flood et al, 2002 Australia **Blue Mountains Eye Study**	1,989	Population-based prospective cohort	5 years	Noninstitutionalized residents aged 49 years or older.	Mean age 64.2 56.9% female 100% white

Author, Year, Country Study Name	N	Study design	Duration	Eligibility criteria	Age Gender Ethnicity
Mares-Perlman et al, 2001 US **Third National Health and Nutrition Examination Survey (NHANES III)**	8,222	Cross-sectional	NA (not prospective)	Stratified probability sample of the civilian noninstitutionalized US population. Certain populaton subgroups, including blacks, Mexican Americans, and adults aged 60 years and older, were oversampled so that stable estimates could be obtained for these groups individually.	Mean age 57 years; 83% white, 8% non-Hispanic blacks, gender not reported.

Author, Year, Country Study Name	N	Study design	Duration	Eligibility criteria	Age Gender Ethnicity
Seddon et al, 1994 US **Eye Disease Case-Control Study**	876 (356 cases, 520 controls)	Case-control	NA (not prospective)	Eligible cases: people ages 55 to 80 years in whom the advanced or exudative neovascular form of AMD was diagnosed within 1 year of their enrollment into the study and who resided in or near the community in which the clinical center was located as defined by ZIP code listing. Control subjects were enrolled concurrently with the case subjects and were selected from a similar pool or outpatients who had undergone a complete dilated ocular examination and did not have the diseases under study. Eligible controls were identified from the same general population and geographic area as the case subjects and resided in or near the community in which the clinical center was located as defined by AIP code listing. Potential controls were identified using the same sources from which he cases were identified.	Mean age 71 (55-80) among cases, 68 (55-80) among controls. 56% of cases, 55% of controls female. Only 6 nonwhites enrolled, analyses were restricted to whites.

Author, Year, Country Study Name	N	Study design	Duration	Eligibility criteria	Age Gender Ethnicity
Snellen et al, 2002 The Netherlands	138 (72 cases, 66 controls)	Case-control	NA (not prospective)	All eligible cases and controls were approached during routine outpatient examinations at the Ophthalmology Department of the University Medical Centre, Nijmegen (The Netherlands) between March 1998 and June 1998. Inclusion criteria for cases: neovascular AMD, age 60 years or older and no diabetes mellitus. Controls selected from the same outpatient clinic: age 60 years or older, no form of AMD, no diabetes mellitus, and no cataracts.	Mean age 76.4 (SD 6.0) among cases, 71.3 (SD 6.6) among controls. 54% of cases, 45% of controls female. Race not reported.

Author, Year, Country Study Name	Exposure: Source/ amount/ duration/ measurement	Comparator	Followup rate
Vandenlangenberg et al, 1998 US **Beaver Dam Eye Study**	Data on the intake of food and supplements from validated 100-item FFQ for two time periods (5 and 15 years prior to disease ascertainment) collected during in-person interviews by trained interviewers. Intake estimated by a composite database that incorporated updated values from the USDA. FFQ modified from the Block NCI Health Habits and History Questionnaire. intake of lutein and zeaxanthin in the past 10 years (food only): Quintile 1: 294 mcg/1000 kcal Quintile 2: 421 mcg/1000 kcal Quintile 3: 537 mcg/1000 kcal Quintile 4: 691 mcg/1000 kcal Quintile 5: 1,005 mcg/1000 kcal	Quintile 1 of the same cohort	81% of known survivors (1709/2110) (79.4% overall, 1709/2152) 2429 invited to participate 2152 completed baseline FFQ 2003 completed baseline FFQ and past diet FFQ 2110 still alive at 5 years 1709 had 5-year followup exam 1689 free of prevalent disease at baseline (not included in analysis) 1657 had evaluable retinal photographs at baseline and f/u 1657 had baseline FFQ 1586 had baseline and past diet FFQ (analyzed)

Evide... Table 1. Observational Studies of Lutein to Reduce ...e Risk of Macular Degeneration

Author, Year, Country Study Name	Exposure: Source/ amount/ duration/ measurement	Comparator	Followup rate
Flood et al, 2002 Australia **Blue Mountains Eye Study**	Validated FFQ sent by mail, brought in by participants to exam. USDA Carotenoid Food Composition database used to estiimate carotenoid intake from the FFQ. FFQ 145-item modified from the Willett questionnaire. Crude mean intake of lutein and zeaxanthin (food only): 829 mcg (SD 497) Quintile 1: 288 mcg/day, 151 mcg/1000 kcal Quintile 2: 510 mcg/day, 259 mcg/1000 kcal Quintile 3: 733 mcg/day, 351 mcg/1000 kcal Quintile 4: 967 mcg/day, 478 mcg/1000 kcal Quintile 5: 1466 mcg/day, 719 mcg/1000 kcal	Quintile 1 of the same cohort	75% of known survivors (2335/3111) 3654 participated in baseline assessment (FFQ and eye exam) 2335 re-examined at 5-year followup (543 died, 383 moved) 3654-543 who died=3111 survivors 2335/3111

Author, Year, Country Study Name	Exposure: Source/ amount/ duration/ measurement	Comparator	Followup rate
Mares-Perlman et al, 2001 US **Third National Health and Nutrition Examination Survey (NHANES III)**	Intake of lutein plus zeaxanthin estimated from FFQ. Carotenoid levels assigned based on the US Department of Agriculture National Cancer Institute Carotenoid Food Composition Database. 10th percentile (ages 40-59): 394 mcg/day 50th percentile (ages 40-59): 1592 mcg/day 90th percentile (ages 40-59): 5554 mcg/day 10th percentile (ages 60-79): 441 mcg/day 50th percentile (ages 60-79): 1640 mcg/day 90th percentile (ages 60-79): 5973 mcg/day 10th percentile (ages ≥80): 382 mcg/day 50th percentile (ages ≥80): 1443 mcg/day 90th percentile (ages ≥80): 5601 mcg/day	High vs low intake in the same cohort	57% of the original targeted sample included in the analysis (persons who had a gradable fundus photograph for ARM, provided food frequency questionnaires, and provided blood for analyses of serum metabolites.

Author, Year, Country Study Name	Exposure: Source/ amount/ duration/ measurement	Comparator	Followup rate
Seddon et al, 1994 US **Eye Disease Case-Control Study**	FFQ Median intake of lutein/zeaxanthin Quintile 1: 560.8 mcg Quintile 2: 1211 mcg Quintile 3: 1708 mcg Quintile 4: 2487 mcg Quintile 5: 5757 mcg	Quintile 1 of the same cohort	82% of eligible cases and 78% of eligible control subjects agreed to participate.

Evide Table 1. Observational Studies of Lutein to Reduce ...e Risk of Macular Degeneration

Author, Year, Country Study Name	Exposure: Source/ amount/ duration/ measurement	Comparator	Followup rate
Snellen et al, 2002 The Netherlands	Data collected in a personal interview using a structured (verbal) questionnaire. Amount of lutein not reported; point scores were assigned to foods based on the amount of lutein and zeaxanthin they contain to determine high and low intake levels.	High vs low intake in the same cohort	4 patients refused to participate (92% response rate)

Evidence Table 1. Observational Studies of Lutein to Reduce the Risk of Macular Degeneration

Author, Year, Country Study Name	Outcomes, Definition	Method and Timing of Outcome Assessment
Vandenlangenberg et al, 1998 US **Beaver Dam Eye Study**	5-year incidence of early ARM lesions: large (>125 mcm) drusen, and retiinal pigmentary abnormalities. Patients were eligible for specific analyses if they did not have specific lesions at baseline. Participants were also categorized as having "any" incident ARM, defined as the presence of either soft, indistinct drusen or of any type of drusen associated with pigmentary abnormalities (increased retinal pigment and depigmentation) at followup when none of these lesions were present at baseline.	Eye exams consisted of taking stereoscopic 30 degree color fundus photographs. Photos graded by persons masked to participant characteristics. Side-by-side comparisons of baseline versus followup photographs were conducted for eyes that showed

Author, Year, Country Study Name	Outcomes, Definition	Method and Timing of Outcome Assessment
Flood et al, 2002 Australia **Blue Mountains Eye Study**	**Early Age-related Maculopathy (ARM)** defined as the absence of AMD and either: (1) large (>125 mcg diameter) indistinct soft or reticular drusen, or (2) both large, distinct, soft drusen and retinal pigmentary abnormalities, within a superimposed grading grid in the macular area. 1) **Incident AMD** defined as presence of AMD in either eye at followup of persons without AMD in both eyes at baseline. 2) **Incident early ARM** was defined as presence of early ARM in either eye at followup of persons without either AMD or early ARM in both eyes at baseline, and also without AMD at followup. 3) **Subjects at risk for incident early ARM** included those who had at baseline distinct soft drusen or retinal pigmentary abnormalities alone, which were not considered as early ARM at the time.	Comprehensive eye exam at baseline and 5-year followup. At both exams, stereoscopic 30 degree retinal photographs of both eyes were taken. ARM grading followed closely the Wisconsin Age-Related Maculopathy Grading System.

Author, Year, Country Study Name	Outcomes, Definition	Method and Timing of Outcome Assessment
Mares-Perlman et al, 2001 US **Third National Health and Nutrition Examination Survey (NHANES III)**	**Soft drusen** defined by their diameter (larger than 63 mcm). **Late ARM** defined as the presence of signs of exudative ARM degeneration or pure geographic atrophy (sharply delineated, roughly round or oval area of apparent absence of the retinal pigment epithelium in which choroidal vessels are more visible than in surrounding areas).	Medical exam took place in a mobile examination center. Protocols for obtaining and grading fundus photographs were adapted from the Wisconsin ARM Grading Scheme.

Table 1. Observational Studies of Lutein to Reduce the Risk of Macular Degeneration

Author, Year, Country Study Name	Outcomes, Definition	Method and Timing of Outcome Assessment
Seddon et al, 1994 US **Eye Disease Case-Control Study**	Diagnostic criteria for AMD included a visual acuity of less than 20/20 in the affected eye or distortion on the Amsler grid, drusen in either eye, and at least one of the following signs of exudative AMD: 1) macular fibrous scar; and/or 2) subretinal hemorrhage or fluorescein angiographic signs of veovascularization with one or more of the following clinical signs involving the macula: a neurosensory detachment, lipid deposits, gray subretinal membrane, or a retinal pigment epithelium detachment.	All cases of AMD were confirmed with an examination by a retina specialist, as well as by fundus photography and fluorescein angiography.

Evid[illegible] Table 1. Observational Studies of Lutein to Reduc[illegible]e Risk of Macular Degeneration

Author, Year, Country Study Name	Outcomes, Definition	Method and Timing of Outcome Assessment
Snellen et al, 2002 The Netherlands	Neovascular AMD; not defined.	Method of determining diagnosis not reported.

Table 1. Observational Studies of Lutein to Reduce Risk of Macular Degeneration

Author, Year, Country Study Name	Results	Confounders controlled for in analysis	Funding source
Vandenlangenberg et al, 1998 US **Beaver Dam Eye Study**	5-year incidence of age-related Maculopathy Adjusted OR (95% CI) **Large drusen (114/1361=8%)** *(intake in the past 10 years)* Quintile 1: 1.0 (referent) Quintile 2: 0.76 (0.4, 1.5) Quintile 3: 0.76 (0.4, 1.5) Quintile 4: 0.93 (0.5, 1.7) Quintile 5: 0.93 (0.5, 1.8) p for trend= 0.86 *(intake in the past year)* Quintile 1: 1.0 (referent) Quintile 2: 0.66 (0.3, 1.3) Quintile 3: 1.04 (0.6, 1.9) Quintile 4: 0.92 (0.5, 1.8) Quintile 5: 0.93 (0.5, 1.8) p for trend= 0.87 **Pigmentary abnormalities (63/1405=5%)** *(intake in the past 10 years)* Quintile 1: 1.0 (referent) Quintile 2: 1.38 (0.6, 3.1) Quintile 3: 1.06 (0.4, 2.6) Quintile 4: 0.53 (0.2, 1.5) Quintile 5: 1.48 (0.6, 3.5) p for trend= 0.68 *(intake in the past year)* Quintile 1: 1.0 (referent) Quintile 2: 0.82 (0.3, 2.0) Quintile 3: 0.92 (0.4, 2.1) Quintile 4: 1.13 (0.5, 2.6) Quintile 5: 0.84 (0.3, 2.0) p for trend= 0.87	Age, sex, total calories, pack-years smoked, beer intake, history of cardiovascular disease, and history of diabetes.	National Institutes of Health and Research to Prevent Blindness.

Author, Year, Country Study Name	Results	Confounders controlled for in analysis	Funding source
Flood et al, 2002 Australia **Blue Mountains Eye Study**	1) Incident AMD: 21 cases (no association with baseline intake, data not reported) 2) Incident Early Age-related Maculopathy Multivariate OR (95% CI) Quintile 1: 1.0 (referent) Quintile 2: 510 mcg: 0.9 (0.5, 1.5) Quintile 3: 733 mcg: 0.8 (0.5, 1.4) Quintile 4: 967 mcg: 0.7 (0.4, 1.3) Quintile 5: 1466 mcg: 1.0 (0.6, 1.6) p for trend= 0.93 3) At risk for incident early ARM: Progression from AREDS category 1 or 2 to 3 or 4: 206/1709 (12%); (analysis based on only 162 who completed FFQ). No association with baseline intake, data not reported.	Age, gender, smoking, family history of ARM, energy.	National Health and Medical Research Council, Canberra, Australia.

Evic e Table 1. Observational Studies of Lutein to Redu he Risk of Macular Degeneration

Author, Year, Country Study Name	Results	Confounders controlled for in analysis	Funding source
Mares-Perlman et al, 2001 US **Third National Health and Nutrition Examination Survey (NHANES III)**	Adjusted odds ratio (95% CI) for soft drusen in high vs low quintiles of lutein and zexanthin in the diet: Total: 1.4 (1.0, 1.8) ages 40-59: 1.2 (0.6, 2.3) ages 60-79: 1.3 (0.9, 1.9) ages ≥80: 2.4 (1.3, 4.4)	Age, gender, alcohol use, hypertension, smoking, and BMI.	NIH and Research to Prevent Blindness

Table 1. Observational Studies of Lutein to Reduce the Risk of Macular Degeneration

Author, Year, Country Study Name	Results	Confounders controlled for in analysis	Funding source
Seddon et al, 1994 US **Eye Disease Case-Control Study**	Adjusted OR (95% CI) for exudative AMD by quintile of energy-adjusted nutrient intake (lutein/zeaxanthin median intake): Quintile 1: 1.0 (referent) Quintile 2: 1.14 (0.7, 1.8) Quintile 3: 0.84 (0.5, 1.3) Quintile 4: 0.77 (0.5, 1.2) Quintile 5: 0.43 (0.2, 0.7) p for trend <0.001	Age, sex, clinic, education, systolic blood pressure, self-reported physical activity level, alcohol intake, BMI, and smoking status.	National Eye Institute

Author, Year, Country Study Name	Results	Confounders controlled for in analysis	Funding source
Snellen et al, 2002 The Netherlands	Adjusted OR (95% CI) for AMD by quartile of intake: Highest: 1.0 (referent) High: 3.4 (0.9, 12.3) Low: 3.6 (1.0, 12.9) Lowest: 5.3 (1.5, 18.4)	Age, cigarette smoking, sunlight exposure, and family history.	Not reported

Evide. Table 2. Internal validity of studies of lutein to redu. the risk of macular degeneration

Author, Year, Country Study Name	Unbiased selection of cohort?	Sufficiently large?	Clear description of cohort?	Appropriate exposure/ intervention measures?	Appropriate measurement of outcomes?
Flood et al, 2002 Australia **Blue Mountains Eye Study**	Yes- census info, 2 postal codes, phone and door-to-door contact.	Yes for ARM--study was powered for maculopathy, not AMD	Yes	Yes	OK for early ARM, but early ARM is not a surrogate for AMD, only a risk factor for AMD
Vandenlangenberg et al, 1998 US **Beaver Dam Eye Study**	Yes	Not clear	Yes	Yes	Ok for early ARM, but early ARM is not a surrogate for AMD, only a risk factor for AMD

Author, Year, Country Study Name	Unbiased selection of cohort?	Sufficiently large?	Clear description of cohort?	Appropriate exposure/ intervention measures?	Appropriate measurement of outcomes?
Mares-Perlman et al, 2001 US **Third National Health and Nutrition Examination Survey (NHANES III)**	Significant differences ($p<0.01$) in the characteristics of participants included compared with those excluded are as follows: participants who were included were less likely to be current smokers (19% vs 24%), but more likely to have smoked in the past (37% vs 30%). A greater proportion of participants were white (83% vs 73%) and fewer were non-Hispanic blacks (8% vs 16%). Included participants were also less likely to have a history of hypertension (47% vs 52%) or diabetes (9% vs 13%). Nutritional characteristics also sometimes varied by includsion status. Levels of vitamin E in the serum were higher in those included compared with those excluded. The dieteary intake of zinc and of lutein plus zeaxanthin was slightly higher in included subjects.	Not clear; power calculation not reported	Yes	No- collection of dietary information was not prospective, measured current lutein/zeaxanthin intake via 24-hour recall.	Yes for ARM and macular soft drusen; AMD not measured.

Table 2. Internal validity of studies of lutein to redu[illegible]he risk of macular degeneration

Author, Year, Country Study Name	Unbiased selection of cohort?	Sufficiently large?	Clear description of cohort?	Appropriate exposure/ intervention measures?	Appropriate measurement of outcomes?
Seddon et al, 1994 US **Eye Disease Case-Control Study**	Yes	Not clear; power calculation not reported	No	No- collection of dietary information was not prospective, based on recall in patients with or without current AMD and therefore subject to bias.	Yes
Snellen et al, 2002 The Netherlands	More case patients were female, smoked, had sunlight exposure, low antioxidant intake and first degree relatives with low visual acuity interpreted as AMD.	Not clear; power calculation not reported	Yes	No- collection of dietary information was not prospective, based on recall in patients with or without current AMD and therefore subject to bias; interview and method of classifying lutein intake not validated.	Details not reported

Table 2. Internal validity of studies of lutein to redu[illegible]he risk of macular degeneration

Author, Year, Country Study Name	Adequate followup period?	Followup rate adequate?	Appropriate statistical and analytical methods and reporting (mutlivariate adjustments)?	Reporting errors?	Overall Quality Rating (A,B,C)
Flood et al, 2002 Australia **Blue Mountains Eye Study**	5 years	No, <80% followup.	Yes	No	B
Vandenlangenberg et al, 1998 US **Beaver Dam Eye Study**	5 years	No, <80% followup.	Yes	No	B

Table 2. Internal validity of studies of lutein to redu[illegible]he risk of macular degeneration

Author, Year, Country Study Name	Adequate followup period?	Followup rate adequate?	Appropriate statistical and analytical methods and reporting (mutlivariate adjustments)?	Reporting errors?	Overall Quality Rating (A,B,C)
Mares-Perlman et al, 2001 US **Third National Health and Nutrition Examination Survey (NHANES III)**	NA, not prospective	NA	Yes	No	C

Table 2. Internal validity of studies of lutein to redu[illegible] the risk of macular degeneration

Author, Year, Country Study Name	Adequate followup period?	Followup rate adequate?	Appropriate statistical and analytical methods and reporting (mutlivariate adjustments)?	Reporting errors?	Overall Quality Rating (A,B,C)
Seddon et al, 1994 US **Eye Disease Case-Control Study**	NA, not prospective	NA	Yes	No	C
Snellen et al, 2002 The Netherlands	NA, not prospective	NA	Yes	Yes- N in text and table does not agree (132/138)	C

Evidence Table 3. External validity of studies of lutein to reduce the risk of macular degeneration

Author, Year, Country Study Name	Sufficiently large?	Gender	Racial/ ethnic groups	Age range	Baseline diet similar to US population?	Other population features	Overall Applicability (external validity) I-III
Flood et al, 2002 Australia **Blue Mountains Eye Study**	Yes	56.7% female	entire cohort: 99% white	49-97 years. Those completing FFQ: mean age 64.2, 31.5% <60, 41.8% 60-69, 22.4% 70-79, 4.2% 80+	Baseline lutein intake may be lower than the average US diet (US<1500 mcg per day, this study highest quintile was 719/1000 kcal per day or 1466 mcg).	Small, limited geographic region.	II
Vandenlangenberg et al, 1998 US **Beaver Dam Eye Study**	Yes	Nutrition subsample: 55.5% female	entire cohort: 99% white	age <55, N=600 (37.6%) 55-64, N=460 (29%) 65-74, N=414 (26.1%) >=75, N=112 (7.1%) entire cohort: mean age 60.6, SD 11.3, range 43-86	Baseline lutein intake similar to the average US diet (US<1500 mcg per day, this study highest quintile was 1005 mcg/1000 kcal, or about 2000-3000 mcg per day [estimated]).	Small, limited geographic region.	II
Mares-Perlman et al, 2001 US **Third National Health and Nutrition Examination Survey (NHANES III)**	Not clear	NR	83% white, 8% non-Hispanic blacks	Mean age 57 years	Levels of vitamin E in serum and dietary intake of zinc and lutein plus zeaxanthin was slightly higher in included vs excluded subjects.		II

Evidence Table 3. External validity of studies of lutein to reduce the risk of macular degeneration

Author, Year, Country Study Name	Sufficiently large?	Gender	Racial/ ethnic groups	Age range	Baseline diet similar to US population?	Other population features	Overall Applicability (external validity) I-III
Seddon et al, 1994 US **Eye Disease Case-Control Study**	Not clear	56% of cases and 55% of controls were female	All but 6 participants were white; analyses were restricted only to whites.	Mean age 71 among cases (55-80), 68 among controls (55-80)	Lutein intake higher than overall US population; median intake of lutein by quintile ranged from 560.8 mcg to 5757 mcg.		II
Snellen et al, 2002 The Netherlands	Not clear	54% of cases and 45% of controls were female	race/ethnicity not reported	Mean age 76.4 years among cases, 71.3 among controls (p=0.0001)	Lutein intake not reported, classified as low-high.	46% of cases also had cataracts. Diagnosed eye diseases among control patients consisted of retinal ablatio (33%), glaucoma (24%), vision control (14%), macular hole (9%), and miscellaneous	I

Evide. Table 4. Observational Studies of Lutein to Reduce the Risk of Cataracts

Author, Year, Country Study Name	N	Study design	Duration	Eligibility criteria	Age Gender Ethnicity
Chasan-Taber et al, 1999 US **Nurses' Health Study**	77,466	Prospective cohort	12 years	Female registered nurses aged 30 to 55 years who resided in any of 11 states and returned a mailed questionnaire on medical history, use of oral contraceptives, and risk factors for cancer and cardiovascular disease. Exclusions: Women who reported a diagnosis of cancer (except nonmelanoma skin cancer) before 1980; at the beginning of each subsequent 2-year time period, excluded women who reported a diagnosis of cancer. <45 years of age in 1980 excluded, added to the analysis as they became 45.	45-71 years old at start. Others included as they reached age 45 during study period 100% women

Author, Year, Country Study Name	N	Study design	Duration	Eligibility criteria	Age Gender Ethnicity
Jacques et al, 2001 US **Nutrition and Vision Project (NVP)** (subset of the **Nurses' Health Study**)	603	Retrospective study nested in a prospective cohort study	13-15 years	Nurses' Health Study cohort members aged 53 to 73 years who resided in the Boston, MA, area, were free of diagnosed cancer other than nonmelanoma skin cancer, had complete dietary data, and had both lenses intact.	Mean age 61 100% women Ethnicity not reported

Author, Year, Country Study Name	N	Study design	Duration	Eligibility criteria	Age Gender Ethnicity
Taylor et al, 2001 US **NVP** (subset of the **Nurses' Health Study)**	603	Retrospective study nested in a prospective cohort study	13-15 years	(Same as Jacques) Nurses' Health Study cohort members aged 53 to 73 years who resided in the Boston, MA, area, were free of diagnosed cancer other than nonmelanoma skin cancer, had complete dietary data, and had both lenses intact.	See Jacques

Table 4. Observational Studies of Lutein to Reduce the Risk of Cataracts

Author, Year, Country Study Name	N	Study design	Duration	Eligibility criteria	Age Gender Ethnicity
Brown et al, 1999 US **Health Professionals Followup Study**	36,644	Prospective cohort	8 years	US male dentists, optomerists, osteopaths, podiatrists, pharmacists, and veterinarians, aged 40-75 years in 1986, who responded to a mailed questionnaire sent in February 1986 that elicited information on age, marital status, height and weight, ancestry, medication use, disease history, physical activity, and diet. Exclusions: Men who did not adequately complete the FFQ; those who reported on the 1986 questionnaire a diagnosis of cancer (except nonmelanoma skin cancer); men <45 years at baseline excluded, followup began as they turned 45 years.	100% male Predominantly white

Author, Year, Country Study Name	N	Study design	Duration	Eligibility criteria	Age Gender Ethnicity
Lyle et al, 1999 US **Beaver Dam Eye Study**	1,354	Population-based, prospective cohort	5 years	Middle-aged and older adults in a primarily Caucasian community in south-central Wisconsin, enrolled in the Beaver Dam Eye Study. The entire population of persons aged 43-84 years residing in Beaver Dam were identified by private census and recruited for the study.	entire cohort: mean age 60.6, SD 11.3, range 43-86 entire cohort: 99% white

Author, Year, Country Study Name	N	Study design	Duration	Eligibility criteria	Age Gender Ethnicity
Valero et al, 2002 Spain	692 (347 cases, 345 controls)	Case-control	NA	Residents of the catchment area of the primary health care center of the town of Burjassot, located on the Mediterranean east coast of Spain. Cases and controls were drawn from patients attending the ophthalmology outpatient clinic at the health care center. Most patients were referred for ophthalmologic checkup by ther general practitioners. Others, already seen by the ophthalmologists, were coming back for routine scheduled visits.	% in age group (years): 55-59: 11.6% of cases, 12% controls 60-64: 24% of cases, 25.2% of controls 65-69: 31.2% of cases, 29.3% of controls 70-74: 33.2% of cases, 33.5% of controls 56.6% female among cases; 60.1% female among controls Race/ethnicity not reported; subjects were residents of one town on the Mediterranean east coast of Spain.

Author, Year, Country Study Name	Exposure: Source/ amount/ duration/ measurement	Comparator: Control or background diet/ source/ amount/ duration/ measurement	Followup rate
Chasan-Taber et al, 1999 US **Nurses' Health Study**	FFQ that assessed usual dietary intake over the past year. Administered by mail at baseline (1980), 1982, 1984, 1986 (1986 FFQ added questions about usual dietary intake during high school). Source: Lutein score from foods only, not supplements. Used nutrient intakes reported on the 1980 dietary questionnaire for followup period 1980-1984 and subsequently, an average of intakes from the 1980 and 1984 FFQs for the followup period from 1984 to 1992. Changes in diet after 1984 were not incorporated. Median lutein and zeaxanthin energy-adjusted intake (mcg) Quintile 1: 1172 Quintile 2: 2064 Quintile 3: 2817 Quintile 4: 6047 Quintile 5: 11,685	Lowest quintile of intake in the same cohort.	Overall followup rate in NHS as of 1992: 90.1% 98,462/102,417 responders completed the 1980 FFQ (96.1%) 81,757/95,458 responders completed 1984 the FFQ (85.6%)

Author, Year, Country Study Name	Exposure: Source/ amount/ duration/ measurement	Comparator: Control or background diet/ source/ amount/ duration/ measurement	Followup rate
Jacques et al, 2001 US **Nutrition and Vision Project (NVP)** (subset of the **Nurses' Health Study**)	FFQ that assessed usual dietary intake and supplement use over the past year. Administered by mail at baseline (1980), 1982, 1984, 1986, and 1990. In addition to FFQs collected as part of the Nurses' Health Study, an additional FFQ administered that included questions on vitamin supplement use as part of the NVP (1993-1995). Data from women who completed 5 FFQs collected between 1980 and 1993-1995 to calculate the average total nutrient intake from food and supplements for each participant. Median lutein and zeaxanthin nutrient quintiles used to define intake (mcg) Quintile 1: NA Quintile 2: 2400 Quintile 3: 3300 Quintile 4: 4300 Quintile 5: 5600	Lowest quintile of intake in the same cohort.	478/603 (79%) included in analysis

Author, Year, Country Study Name	Exposure: Source/ amount/ duration/ measurement	Comparator: Control or background diet/ source/ amount/ duration/ measurement	Followup rate
Taylor et al, 2001 US **NVP** (subset of the **Nurses' Health Study)**	(Same as Jacques) FFQ that assessed usual dietary intake and supplement use over the past year. Administered by mail at baseline (1980), 1982, 1984, 1986, and 1990. In addition to FFQs collected as part of the Nurses' Health Study, an additional FFQ administered that included questions on vitamin supplement use as part of the NVP (1993-1995). Data from women who completed 5 FFQs collected between 1980 and 1993-1995 to calculate the average total nutrient intake from food and supplements for each participant. Meidan lutein and zeaxanthin nutrient quintiles used to define intake (mcg) Quintile 1: NA Quintile 2: 2400 Quintile 3: 3300 Quintile 4: 4300 Quintile 5: 5600	Lowest quintile of intake in the same cohort.	492/603 (82%) included in the analysis (excluded 76 because they reported a history of cataracts, 9 with a confirmed history of diabetes by 1990, 19 had incomplete, questionable, or missing lens data, and 7 for whom information about covariates was missing.

Table 4. Observational Studies of Lutein to Reduc[illegible]e Risk of Cataracts

Author, Year, Country Study Name	Exposure: Source/ amount/ duration/ measurement	Comparator: Control or background diet/ source/ amount/ duration/ measurement	Followup rate
Brown et al, 1999 US **Health Professionals Followup Study**	FFQ mailed at baseline (1986). Questions about vitamin and mineral supplement use and average frequency of consumption of a given unit or portion size for each of 131 food items during the previous year. Intake scores were calculated by summing the nutrient contribution of each food multiplied by its frequency of use, using food-composition data from the USDA, food manufacturers, and other published sources. Baseline values for nutrients and other exposures were carried forward throughout the followup period. Median lutein and zeaxanthin median intake (mcg) Quintile 1: 1300 Quintile 2: 2279 Quintile 3: 3182 Quintile 4: 4342 Quintile 5: 6871	Lowest quintile of intake in the same cohort.	Overall followup rate in the HPFS? 36,644 included in the analysis 2107 excluded for inadequate completion of FFQ, others not eligible (prior diagnosis of cancer, <45 years of age)

Table 4. Observational Studies of Lutein to Reduce the Risk of Cataracts

Author, Year, Country Study Name	Exposure: Source/ amount/ duration/ measurement	Comparator: Control or background diet/ source/ amount/ duration/ measurement	Followup rate
Lyle et al, 1999 US **Beaver Dam Eye Study**	In-person interview approximately one month following the baseline examination. Participants asked about their usual diet and use of supplements over the past year. The same information was solicited regarding dietary habits corresponding to 10 years before the interview. Diet was assessed using a 100-item FFQ. For each supplement reported, information was collected on the brand, frequency of use, and amount of nutrient per pill. Carotenoid values reflect intakes from food alone, because supplements did not contain these carotenoids during the time periods studied (1988-1990). Median lutein intake (mcg) Quintile 1: 298 Quintile 2: 459 Quintile 3: 600 Quintile 4: 784 Quintile 5: 1245	Lowest quintile of intake in the same cohort.	1709/2152 (79%) followed up at 5 years (29 could not be located or had moved, 202 had died, 212 declined evaluation)

Table 4. Observational Studies of Lutein to Reduce the Risk of Cataracts

Author, Year, Country Study Name	Exposure: Source/ amount/ duration/ measurement	Comparator: Control or background diet/ source/ amount/ duration/ measurement	Followup rate
Valero et al, 2002 Spain	Questionnaires administered by trained interviewers. Dietary intake data collected via FFQ, using a Spanish version of the Harvard questionnaire. Blood samples taken but lutein was not among the nutrients measured in serum. Quintile 1: ≤ 443 mcg/day Quintile 2: >443-669 mcg/day Quintile 3: >669-993 mcg/day Quintile 4: >993-1383 mcg/day Quintile 5: >1383 mcg/day	Both eyes had LOCS II grading=0; controls frequency matched by age and gender.	4 cases and 11 controls did not attend interviews or blood collection and were excluded.

Author, Year, Country Study Name	Outcomes, Definition	Method and Timing of Outcome Assessment
Chasan-Taber et al, 1999 US **Nurses' Health Study**	Cataract extraction. Excluded cataracts considered by physicians to be either congenital or secondary to chronic steroid use, chronic intraocular inflammaiton, ocular trauma, previous intraocular surgery, or glaucoma.	Patients asked on a questionnaire if they had had a cataract extraction in 1984, 1986, 1988, 1990, or 1992, and if so, for permission to review their medical records. Ophthalmologist contacted to confirm occurrence and dates of extraction and to determine any known cause of the cataract, date of initial diagnosis, and the participant's best corrected visual acuity in both eyes before surgery. Also collected information about location of the lens opacity in each eye with location defined as nuclear, cortical, posterior subcapsular, or any combination of the 3.

Author, Year, Country Study Name	Outcomes, Definition	Method and Timing of Outcome Assessment
Jacques et al, 2001 US **Nutrition and Vision Project (NVP)** (subset of the **Nurses' Health Study**)	Nuclear lens opacities. Lens Opacity Classification System III (LOCS III). Nuclear opacities defined as nuclear opalescence grade 2.5 or higher.	Detailed eye examination using standardized techniques. Color film images taken with a photograhic slitlamp and film to assess the degree of nuclear color and opalescence. LOCS III used to measure the degree of nuclear opalescence. Two individual graders scored each photo and then compared scores and arrived at a consensus score.

Author, Year, Country Study Name	Outcomes, Definition	Method and Timing of Outcome Assessment
Taylor et al, 2001 US **NVP** (subset of the **Nurses' Health Study)**	Cortical or posterior subcapsular lens opacities. Lens Opacity Classification System III (LOCS III). Eyes considered to have opacities if the LOCS III cortical opalescence grade was 0.5 or greater or the posterior subcapsular grade was 0.3 or greater.	(Same as Jacques) Detailed eye examination using standardized techniques. Color film images taken with a photograhic slitlamp and film to assess the degree of nuclear color and opalescence. LOCS III used to measure the degree of nuclear opalescence. Two individual graders scored each photo and then compared scores and arrived at a consensus score.

Table 4. Observational Studies of Lutein to Reduce the Risk of Cataracts

Author, Year, Country Study Name	Outcomes, Definition	Method and Timing of Outcome Assessment
Brown et al, 1999 US Health Professionals Followup Study	Cataract extraction.	Followup questionnaires sent in 1988, 1990, 1992, and 1994 to determine if they had a cataract extraction. Data on extraction confirmed by medical record review.

Author, Year, Country Study Name	Outcomes, Definition	Method and Timing of Outcome Assessment
Lyle et al, 1999 US **Beaver Dam Eye Study**	Incident cataract. Participants classified as having an incident cataract if they were free of severe nuclear opacification (i.e., both lenses at opacity levels 1-3) and had not had prior cataract surgery at baseline, and had at least one lens with severe nuclear opacification (opacity level 4 or 5) at the followup examination.	Nuclear opacities graded from photographs on a 5-step ordinal scale using a set of standard photographs for comparison; independent assessments by 2 graders who were unaware of subject characteristics.

Author, Year, Country Study Name	Outcomes, Definition	Method and Timing of Outcome Assessment
Valero et al, 2002 Spain	Case defined as any patient between ages 55 and 74 years, diagnosed with nuclear, cortical, posterior subcapsular, or mixed cataract (any combination of these) in at least one eye and LOCS II grade 1 or greater. Controls with both eyes of LOCS II grading =0.	Cases identified through a primary health care referral center among patients attending the ophthalmology outpatient clinic over a 14-month period.

Table 4. Observational Studies of Lutein to Reduce the Risk of Cataracts

Author, Year, Country Study Name	Results	Confounders controlled for in analysis	Funding source
Chasan-Taber et al, 1999 US **Nurses' Health Study**	Multivariate RR (95% CI) Quintile 1: 1.0 (referent) Quintile 2: 1.01 (0.86, 1.19) Quintile 3: 0.95 (0.80, 1.11) Quintile 4: 0.81 (0.69, 0.96) Quintile 5: 0.88 (0.75, 1.03) p for trend= 0.04	Age, time period, diagnosis of diabetes, cigarette smoking, BMI, area of residence, number of physician visits, aspirin use, total entergy intake, alcohol use.	National Eye Institute, National Cancer Institute

Author, Year, Country Study Name	Results	Confounders controlled for in analysis	Funding source
Jacques et al, 2001 US **Nutrition and Vision Project (NVP)** (subset of the **Nurses' Health Study**)	Nuclear lens opacities Adjusted OR (95% CI) Quintile 1: 1.0 (referent) Quintile 2: 0.45 (0.24, 0.84) Quintile 3: 0.49 (0.25, 0.94) Quintile 4: 0.39 (0.21, 0.72) Quintile 5: 0.52 (0.29, 0.91) p for trend= 0.08	Age at examination, pack-years smoked through 1990, history of hypertension through 1990, body mass index in 1980, summer sunlight exposure in 1980, and usual alcohol intake between 1980 and the date of the examination.	US Department of Agriculture, National Research Initiative Competitive Grant Program, the Brigham Surgical Group, National Eye Institute, National Institutes of Health, and Florida Department of Citrus.

Author, Year, Country Study Name	Results	Confounders controlled for in analysis	Funding source
Taylor et al, 2001 US **NVP** (subset of the **Nurses' Health Study)**	Cortical lens opacities Adjusted OR (95% CI) Quintile 1: 1.0 (referent) Quintile 2: 0.63 (0.38, 1.05) Quintile 3: 1.30 (0.78, 2.15) Quintile 4: 1.02 (0.62, 1.67) Quintile 5: 0.86 (0.52,1.44) p for trend (NS) Posterior subcapsular lens opacities Adjusted OR (95% CI) Quintile 1: 1.0 (referent) Quintile 2: 0.61 (0.30, 1.25) Quintile 3: 0.83 (0.41, 1.68) Quintile 4: 0.29 (0.12, 0.70) Quintile 5: 0.60 (0.28, 1.30) p for trend (NS)	Age at examination, pack-years smoked through 1990, history of hypertension through 1990, body mass index in 1980, summer sunlight exposure in 1980, and usual alcohol intake between 1980 and the date of the examination.	US Department of Agriculture, National Research INitiative Competitive Grant Program, the Brigham Surgical Group, National Institutes of Health, Florida Department of Citrus, Roche Vitamins.

Author, Year, Country Study Name	Results	Confounders controlled for in analysis	Funding source
Brown et al, 1999 US **Health Professionals Followup Study**	Multivariate RR (95% CI) Quintile 1: 1.0 (referent) Quintile 2: 1.00 (0.81, 1.23) Quintile 3: 0.98 (0.79, 1.20) Quintile 4: 0.83 (0.67, 1.04) Quintile 5: 0.81 (0.65, 1.01) p for trend= 0.03	Age, time period, diagnosis of diabetes, cigarette smoking, BMI, area of US residence, aspirin use, energy intake, physical activity, alcohol intake, routine eye exams, and profession.	National Institutes of Health

Author, Year, Country Study Name	Results	Confounders controlled for in analysis	Funding source
Lyle et al, 1999 US **Beaver Dam Eye Study**	Adjusted OR (95% CI) by intake at baseline (1988-1990): Quintile 1: 1.0 (referent) Quintile 2: 0.90 (0.60, 1.50) Quintile 3:1.00 (0.60, 1.70) Quintile 4: 1.00 (0.60, 1.60) Quintile 5: 0.70 (0.40, 1.10) p for trend= 0.10 by intake in distant past (1978-1980): Quintile 1: 1.0 (referent) Quintile 2: 0.90 (0.60, 1.60) Quintile 3: 0.90 (0.60, 1.70) Quintile 4: 0.70 (0.40, 1.20) Quintile 5: 0.50 (0.30, 0.80) p for trend= 0.002	Age, energy intake, pack-years of smoking, reported amount of alcohol consumed per week.	National Eye Institute and Research to Prevent Blindness foundation.

Author, Year, Country Study Name	Results	Confounders controlled for in analysis	Funding source
Valero et al, 2002 Spain	Risk of cataract OR (95% CI): Quintile 1: 1.0 (referent) Quintile 2: 0.88 (0.54, 1.42) Quintile 3: 0.98 (0.61, 1.56) Quintile 4: 0.69 (0.40, 1.09) Quintile 5: 1.00 (0.64, 1.64) p for trend= 0.78	Sex, age, and energy intake.	Nutricia Foundation, The Netherlands; and the Spanish Ministry of Health.

Evidence Table 5. Internal validity of studies of lutein to reduce the risk of cataracts

Author, Year, Country Study Name	Unbiased selection of cohort?	Sufficiently large?	Clear description of cohort?	Appropriate exposure/ intervention measures?	Appropriate measurement of outcomes?	Adequate followup period?
Chasan-Taber et al, 1999 US **Nurses' Health Study**	Yes	Yes	Yes	Yes	Yes	Yes
Jacques et al, 2001 US **Nutrition and Vision Project** (subset of the **Nurses' Health Study**)	Yes	Yes	Yes	Yes	Yes	Yes
Taylor et al, 2001 US **Nutrition and Vision Project** (subset of the **Nurses' Health Study**)	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 5. Internal validity of studies of lutein to reduce the risk of cataracts

Author, Year, Country Study Name	Unbiased selection of cohort?	Sufficiently large?	Clear description of cohort?	Appropriate exposure/ intervention measures?	Appropriate measurement of outcomes?	Adequate followup period?
Brown et al, 1999 **Health Professionals Followup Study**	Yes	Yes	Yes	Yes	Yes	8 years, adequate
Lyle et al, 1999 **Beaver Dam Eye Study**	Yes	Yes	Yes	Single FFQ, moderate	Possibly inappropriate measure, subject to bias	5 years, moderate
Valero et al, 2002 Spain	Yes	Unknown, sample size calculated not calculated for lutein intake.	Yes	No, collection of dietary data not prospective.	Yes	NA

Evidence Table 5. Internal validity of studies of lutein to reduce the risk of cataracts

Author, Year, Country Study Name	Followup rate?	Appropriate statistical and analytical methods and reporting (mutlivariate adjustments)?	Reporting errors?	Overall Quality Rating (A,B,C)
Chasan-Taber et al, 1999 US **Nurses' Health Study**	Overall NHS cohort, 1992: 90.1%	Yes	No	A
Jacques et al, 2001 US **Nutrition and Vision Project** (subset of the **Nurses' Health Study**)	Overall NHS cohort, 1992: 90.1%	Yes	No	A
Taylor et al, 2001 US **Nutrition and Vision Project** (subset of the **Nurses' Health Study**)	Overall NHS cohort, 1992: 90.1%	Yes	No	A

Evidence Table 5. Internal validity of studies of lutein to reduce the risk of cataracts

Author, Year, Country Study Name	Followup rate?	Appropriate statistical and analytical methods and reporting (mutlivariate adjustments)?	Reporting errors?	Overall Quality Rating (A,B,C)
Brown et al, 1999 **Health Professionals Followup Study**	Inadequate reporting	Yes	No	A
Lyle et al, 1999 **Beaver Dam Eye Study**	High loss (24.5% lost to followup, no data on dropouts)	Yes	No	C
Valero et al, 2002 Spain	NA	Yes	No	C

Evidence Table 6. External validity of studies of lutein to reduce the risk of cataracts

Author, Year, Country Study Name	Sufficiently large?	Gender	Racial/ ethnic groups	Age range	Baseline diet similar to US population?	Other population features	Overall Applicability (external validity) I-III
Chasan-Taber et al, 1999 US **Nurses' Health Study**	Yes	100% female	Predominantly white	45-71 years old at start. Others included as they reached age 45 during study period	Unable to assess	Nurses only	II
Jacques et al, 2001 US **Nutrition and Vision Project** (subset of the **Nurses' Health Study**)	Yes	100% female	Predominantly white	Mean age 61	Unable to assess	Nurses only	II
Taylor et al, 2001 US **Nutrition and Vision Project** (subset of the **Nurses' Health Study**)	Yes	100% female	Predominantly white	Mean age 61	Unable to assess	Nurses only	II
Brown et al, 1999 US **Health Professionals Followup Study**	Yes	100% male	Predominantly white	100% male Predominantly white	Unable to assess	Health professionals only	II
Lyle et al, 1999 US **Beaver Dam Eye Study**	Yes	Nutrition subsample: 55.5% female	Predominantly white	Entire cohort: mean age 60.6, SD 11.3, range 43-86	Unable to assess	Small, limited geographic region.	II

Evidence Table 6. External validity of studies of lutein to reduce the risk of cataracts

Author, Year, Country Study Name	Sufficiently large?	Gender	Racial/ ethnic groups	Age range	Baseline diet similar to US population?	Other population features	Overall Applicability (external validity) I-III
Valero et al, 2002 Spain	Unknown	56.6% female among cases; 60.1% female among controls	Race/ethnicity not reported.	% in age group (years): 55-59: 11.6% of cases, 12% controls 60-64: 24% of cases, 25.2% of controls 65-69: 31.2% of cases, 29.3% of controls 70-74: 33.2% of	No; Mediterranean diet presumed higher in antioxidants than the US population	Residents of one town on the Mediterranean east coast of Spain.	II